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Survival and Outcome of Patients With Urea Cycle Disorders: A Single-Center Experience

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Abstract

Background: Urea cycle disorders (UCDs) are inborn errors of ammonia detoxification. Ammonia is detoxified by its conversion to urea in the liver.

Aim: To evaluate the spectrum of UCDs and the outcome of patients with UCDs in India

Materials and Methods: This was a retrospective study of patients with UCDs who presented to our center during 2000 to 2016. We biochemically suspected a UCD in 59 patients (34 males and 25 females) who had typical clinical symptoms. Presence of UCD was confirmed in 36 (24 males and 12 females) patients by molecular studies.

Results: Molecular diagnosis showed presence of citrullinemia type I in 23 patients, argininosuccinic aciduria in 6, ornithine transcarbamylase deficiency (OTCD) in 3, carbamoyl phosphate synthetase 1 deficiency in 1, N-acetyl glutamate synthase deficiency in 2, and arginase deficiency (ARGD) in 1.

Of the 36 patients with confirmed UCD, 23 died (63.9% mortality), 3 were lost to follow-up, and 10 (5 with argininosuccinate synthetase deficiency, 1 with argininosuccinate lyase deficiency, 3 with OTCD, and 1 with ARGD) are being followed up regularly and have good metabolic control.

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Conclusion: In India, owing to the absence of newborn screening, UCDs are detected only after development of symptoms, resulting in a high rate of morbidity and mortality (23 of 36 patients died). Citrullinemia type I is the commonest UCD (detected in 23 of 36 patients), with the common mutation p.Gly390Arg seen in more than half of the patients with the disorder (52.17%). Early and aggressive treatment has resulted in good outcome in only 2 patients, while 4 were mildly affected. Of those alive, 50% have epilepsy, 40% have cerebral palsy, and 40% have neurobehavioral problems.

Key Words: Urea cycle disorder, hyperammonemia, citrullinemia, argininemia, ornithine transcarbamylase deficiency, argininosuccinic aciduria, carbamoyl phosphate synthetase 1 deficiency, N-acetyl glutamate synthase deficiency, hyperornithinemia–hyperammonemia–homocitrullinuria syndrome

Introduction

Urea cycle disorders (UCDs) are inborn errors of ammonia detoxification. Ammonia that is produced from amino acid metabolism is detoxified mainly through its conversion to urea in the liver (Figure). The enzymes involved in UCDs are carbamoyl phosphate synthetase 1 (CPS1), N-acetyl glutamate synthase (NAGS), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase, and arginase. Often, infants with a UCD initially appear normal but can rapidly develop cerebral edema and the related signs including lethargy, vomiting, feeding difficulties, hyperventilation or hypoventilation, hypothermia, seizures, neurologic posturing, and coma.[1] The incidence of these disorders in the United States has been estimated to range from 1:14,000 for ornithine transcarbamylase deficiency (OTCD) to 1:3,50,000 for arginase deficiency (ARGD).[2] A recent study found an overall incidence of 1:35,000.[3] However, in India, since formal nationwide newborn screening (NBS) is not available, data regarding the incidence of UCD are not available. In our practice, we have come across 36 of 833 (4.32%) critically ill newborns with a biochemical profile suggesting a UCD.[4] Though this does not indicate the incidence of UCD in the Indian population, it provides an idea about the incidence of UCDs among critically ill newborns.

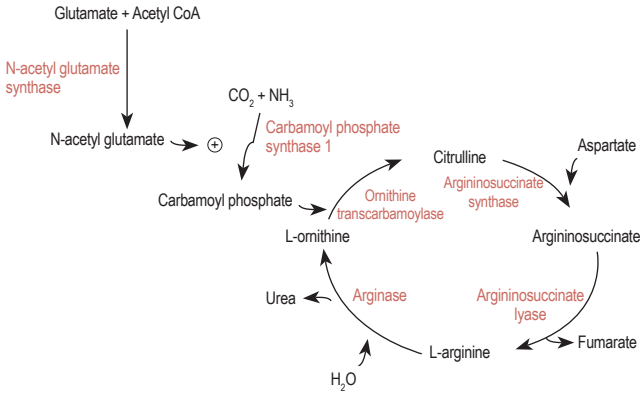

Figure. The Urea Cycle

Aim

To evaluate the spectrum of UCDs and outcome of patients with UCDs in a single, large center in India for identifying areas that need attention in order to improve the outcome of patients with UCD in India

Materials and Methods

This was a retrospective study of patients with UCDs who presented to the Navi Mumbai Institute of Research in Mental and Neurological Handicap (NIRMAN; Navi Mumbai, Maharashtra, India) from 2000 to 2016. Based on the biochemical profile, we suspected the presence of a UCD in 59 patients (34 males and 25 females) presenting with hyperammonemia, vomiting, convulsions, failure to thrive, and lethargy. Among the entire cohort, 36 patients were confirmed to have a UCD by molecular studies. Of these, 24 were males and 12 were females (Table 1). Clinically and biochemically, N-acetyl glutamate synthase deficiency (NAGSD) or carbamoyl phosphate synthetase 1 deficiency (CPS1D) was suspected in 9 patients, but it could not be confirmed by mutation analysis. Hyperornithinemia–hyperammonemia–homocitrullinuria syndrome was suspected in 2 patients and lysinuric protein intolerance was suspected in 1 patient. However, these also could not be confirmed by gene sequencing. One family with 2 neonatal deaths with early-onset hyperammonemic encephalopathy was also included in our cohort. No gene studies were performed in the index cases. The parents were screened and found to be carriers for NAGS mutations.

Biochemical analysis was performed for each patient at our center. Ammonia was analyzed by dry chemistry (VITROS Chemistry System, Johnson & Johnson Clinical Diagnostics, NJ, USA/Fujifilm Dri Chem NX500i, Tokyo, Japan). Urinary orotic acid was quantified using high-performance liquid chromatography (Waters Corporation, MA, USA); amino acids in plasma and urine were quantified using ultra–high-performance liquid chromatography (UHPLC) (Agilent Technologies, 1200 Infinity Series, CA, USA). Argininosuccinic acid quantitation was also done using UHPLC (Agilent Technologies) in patients with elevated levels of citrulline to rule out argininosuccinic aciduria (ASA). Follow-up was performed using the same analytical techniques and, in some cases, tandem mass spectrometry using dried blood spots.

Molecular studies were performed in each patient for confirmation of the presence of UCD. Gene sequencing was done at Zurich University (Zurich, Switzerland) by standard methods. In brief, for analysis of the *ASS1*, *ASL*, *OTC*, or *ARG* genes, DNA from peripheral blood cells was used for exon-wise polymerase chain reaction amplification followed by sequencing. For *CPS1* analysis, RNA was isolated from lymphocytes after a short-time culture in the presence of phytohemagglutinin followed by reverse transcription polymerase chain reaction and sequencing of fragments of the *CPS1* transcript.[5] Identified mutations were confirmed in parental DNA whenever this was available. Multiplex ligation-dependent probe amplification or deletion/duplication studies were not done in this cohort. Mutation testing was done after informed consent was obtained from the parents or legal guardians.

Results

Of the 59 patients who were clinically and biochemically suspected to have a UCD, presence of a UCD was confirmed in 36 by molecular studies. Molecular diagnosis confirmed citrullinemia type I in 23 patients, ASA in 6, OTCD in 3, CPS1D in 1, NAGSD in 2, and argininemia in 1. No mutations could be identified in 23 of 59 patients. Of these, 7 patients were suspected to have OTCD. Findings on gene sequencing for OTCD in these patients were normal; however, deletion/duplication studies were not performed.

In our cohort of 36 patients with confirmed UCD, 23 died, 3 were lost to follow-up, and 10 are being followed up in our clinic with regular clinical and biochemical monitoring. Patient details are provided in Table 1.

Of the 23 patients with argininosuccinate synthase deficiency (ASSD), 15 died, 3 were lost to follow-up, and 5 are alive. Of the 6 patients with argininosuccinate lyase deficiency (ASLD), 5 died and only 1 is alive and under irregular follow-up. All 3 patients with OTCD are alive and are under regular follow-up. Both the patients with NAGSD died. The patient with ARGD is alive and the patient with CPS1D died. Overall, 10 patients are being followed up regularly.

Table 1. Distribution of the Cohort According to Sex and Outcome in Each Disorder

Disorder	Number of Patients, n	Male, n	Female, n	Alive, n	Dead, n	Lost To Follow-up, n
ASSD	23	13	10	5	15	3
ASLD	6	5	1	1	5	0
OTCD	3	2	1	3	0	0
NAGSD	2	2	0	0	2	0
ARGD	1	1	0	1	0	0
CPS1D	1	1	0	0	1	0
Total	36	24	12	10	23	3

ARGD, arginase deficiency; ASLD, argininosuccinate lyase deficiency; ASSD, argininosuccinate synthase deficiency; CPS1D, carbamoyl phosphate synthetase 1 deficiency; NAGSD, N-acetyl glutamate synthase deficiency; OTCD, ornithine transcarbamylase deficiency.

In our cohort, all the patients with citrullinemia presented in the early newborn period. Age at presentation ranged from 1 day to 4 months, with a mean of 14 days (Table 2). Five patients with ASLD presented in the newborn period (< 7 d) and 1 patient presented at 2 years of age. All 3 patients with OTCD and 1 with ARGD presented around 2 years of age. The patient with CPS1D presented at the age of 1 month.

Of the 36 patients, 31 presented in the neonatal period before 4 weeks of life (86.11%) and only 5 presented after 4 weeks of life. The mortality rate in the neonatal presenters was 71% (22 of 31) and it was 20% in those who had late-onset presentation (1 of 5) (Table 3).

In patients 35 and 36, no investigations were performed. Both were siblings and died of hyperammonemia in the neonatal period. Parents were screened molecularly and were found to be carriers of mutation p.Gln331* in exon 4 of the NAGS gene.

Neurologic outcomes of patients

Table 4 shows the degree of neurologic outcomes.

Normal neurologic outcome (2 of 10)

Normal mental and physical development was seen in 1 male patient with OTCD (patient # 31). This child is treated with sodium benzoate at a dose of 250 mg/kg/d, arginine at a dosage of 250 mg/kg/d, and protein restriction. Because of the financial constraints, parents cannot afford special formulas.

Table 3. Mortality in Neonatal and Late-Onset Presenters

Disorder	Neonatal Presenters, n	No. of Patients Who Died, n	Late-Onset Presenters, n	No. of Patients Who Died, n
ASSD	23	15	0	0
ASLD	5	4	1	1
OTCD	0	0	3	0
NAGSD	2	2	0	0
ARGD	0	0	1	0
CPS1D	1	1	0	0
Total	31	22 (71%)	5	1 (20%)

ARGD, arginase deficiency; ASLD, argininosuccinate lyase deficiency; ASSD, argininosuccinate synthase deficiency; CPS1D, carbamoyl phosphate synthetase 1 deficiency; NAGSD, N-acetyl glutamate synthase deficiency; OTCD, ornithine transcarbamylase deficiency.

One child with ASSD (male, patient # 12) who received a transplant at the age of 6 months also has normal milestones without any seizure disorders. Although this child has persistently elevated levels of citrulline on follow-up (mean citrulline level = 1,800 μmol/L), he does not have episodes of hyperammonemia.

Mild neurologic disorder (4 of 10)

Four patients (2 with ASSD: 1 male, patient # 5 and 1 female, patient # 22 and 2 with OTCD: 1 male, patient # 30 and 1 female, patient # 32) have milder neurologic outcome. Two patients with citrullinemia type I (1 male, patient # 5 and 1 female, patient # 22) have normal physical development. They have achieved normal motor and mental milestones but have hyperactivity disorder, learning disabilities, and behavioral problems. The male child also had episodes of seizures, which was successfully treated with levetiracetam, and findings on electroencephalogram (EEG) were abnormal. The female child required medication for hyperactivity disorder for 2 years. No seizures or abnormal findings on EEG were detected. A formal psychologic evaluation was not performed.

Table 2. Patient Information Including the Mutations and Outcome

Patient Number	Age at Onset	Sex	Exon	Nucleotide Change	Protein Change	Outcome
ASSD						
1	3 d	Male	15	c.1168G>A	p.Gln390Arg	Died
2	5 d	Male	15	c.1168G>A	p.Gln390Arg	Died
3	3 d	Female	7	c.470G>A	p.Arg157His	Alive (epilepsy, severe mental retardation, and bed ridden)
4	2 d	Male	15	c.1168G>A	p.Gln390Arg	Died
5	1 d	Male	15	c.1168G>A	p.Gln390Arg	Alive (H/o epilepsy, treated with levetiracetam, ADHD; now physically normal with learning disabilities and hyperactivity)
6	2 d	Female	15	c.1168G>A	p.Gln390Arg	Died
7	6 d	Female	15	c.1139delA	p.Gln380Argfs*19	Died
8	6 d	Female	15	c.1168G>A	p.Gln390Arg	Died
9	7 d	Male	15	c.1168G>A	p.Gln390Arg	Died
10	4 d	Male	15	c.1168G>A	p.Gln390Arg	Died
11	6 d	Female	13	c.190C>T	p.Arg304Trp	Died
12	16 d	Male	15	c.1168G>A	p.Gln390Arg	Alive (normal physical and mental development, on normal diet, liver Tx at the age of 6 mo)
13	2 d	Female	12	c.815G>A	p.Arg272His	Lost to follow-up
14	4 mo	Female	14,15	c.1088G>A, c.1168G>A	p.Arg363Gln, p.Gly390Arg	Lost to follow-up
15	5 d	Male	5	c.269G>A	p.Gly90Asp	Died
16	4 mo	Male	15	c.1168G>A	p.Gln390Arg	Died
17	2 d	Male	7	c.470G.A	p.Arg157His	Alive (severe developmental delay and mental retardation; H/o seizure disorder)
18	6 d	Male	15	c.1168G>A	p.Gln390Arg	Died
19	8 d	Female	15	c.1168G>A	p.Gln390Arg	Died
20	7 d	Female	12	c.793C>T	p.Arg265Cys	Lost to follow-up
21	5 d	Male	13	c.910C>T	p.Arg304Trp	Died
22	1 d	Female	6, 7	c.370G>A,c.470C>A	p.Asp124Asn, p.Arg157His	Alive (physically normal with learning disabilities and hyperactivity)
23	2 d	Male	7	c.470G>A	p.Arg157His	Died

Contd.

Table 2. *Contd.*

ASLD						
24	2 y	Male	15	c.1153C>T	p.Arg385Cys	Died (the child was developing normally with slight learning difficulty, was attending regular school; he died at the age of 11 y due to severe dengue infection)
25	2 d	Male	4	c.337C>T	p.Arg113Trp	Died
26	2 y	Female	4	c.337C>T	p.Arg113Trp	Alive (delayed physical and mental milestones with hepatomegaly and abnormal LFT; H/o seizure disorders and poor follow-up; suggested liver Tx)
27	2 d	Male	11	c.857A>G	p.Gln286Arg	Died
28	5 d	Male	12	c.967A>G	p.Lys323Glu	Died
29	4 d	Male	8	c.649C>T	p.Arg217*	Died
OTCD						
30	5.5 y	Male	6	c.604C>T	p.His202Tyr	Alive (normal physical development, with near-normal milestones, episodic hyperammonemia and behavioral abnormalities with ADHD)
31	3 y	Male	4	c.386G>A	p.Arg129His	Alive (normal physical and mental milestones and no ADHD or behavioral abnormalities)
32	2 y	Female	7	c.674C>T	p.Pro225Leu	Alive (episodic hyperammonemia, delayed motor and mental milestones, and ADHD)
ARGD						
33	12 y	Male	1	c.2T>C	p.Met1Thr	Alive (severe spastic diplegia, grossly delayed milestones, and behavior abnormality)
CPS1D						
34	1 mo	Male	19	c.2339G>A	p.Arg780His	Died
NAGSD						
35	7 d	Male	—	—	—	Died

Contd.

Table 2. *Contd.*

36	2 d	Male	—	—	—	Died

ADHD, attention-deficit/hyperactivity disorder; ARGD, arginase deficiency; ASLD, argininosuccinate lyase deficiency; ASSD, argininosuccinate synthase deficiency; CPS1D, carbamoyl phosphate synthetase 1 deficiency; H/o, history of; NAGSD, N-acetyl glutamate synthase deficiency; OTCD, ornithine transcarbamylase deficiency; Tx, transplant.

Table 4. Degree of Neurologic Deficit in 10 Cases

Degree of Neurologic Deficit	Disorders	Number (Out of Those Alive, n=10)
No Neurologic Deficit	OTCD	1
	ASSD	1
Mild-to-moderate Neurologic Deficit	ASSD	2
	OTCD	2
Severe Neurologic Deficit	ASSD	2
	ASLD	1
	ARGD	1

ARGD, arginase deficiency; ASLD, argininosuccinate lyase deficiency; ASSD, argininosuccinate synthase deficiency; OTCD, ornithine transcarbamylase deficiency.

Two children with OTCD (1 male, patient # 30 and 1 female, patient # 32) have normal physical development. The male child, who is now 11 years old, has achieved milestones but has attention-deficit/hyperactivity disorder and stubborn behavior. He has had 2 to 3 episodes of hyperammonemia requiring peritoneal dialysis. However, since 1 year, after the initiation of treatment with sodium benzoate at a dosage of 250 mg/kg/d and arginine at a dosage of 250 mg/kg/d and a special diet, he is keeping well. The female child has been recently diagnosed with OTCD and has mildly delayed mental milestones; treatment with sodium benzoate at a dosage of 250 mg/kg/d, arginine at a dosage of 150 mg/kg/d, and citrulline at a dosage of 150 mg/kg/d has been initiated. She recently had seizure episodes of hyperammonemia associated with enteric fever.

Severe neurologic disorder (4 of 10)

Four patients have severe neurologic sequelae. Of these, 2 have ASSD (1 male, patient # 17 and 1 female, patient # 3), 1 has ASLD (female, patient # 26), and 1 has ARGD (male, patient # 33). Both the patients with ASSD have severe developmental delay with seizure disorder.

The child with ASLD has delayed motor and mental milestones with hepatomegaly and abnormal findings on liver function tests (LFTs). She has episodic hyperammonemia and has been advised liver transplantation.

The child with ARGD has grossly delayed milestones, is nonambulatory, with spastic paraplegia and multiple seizure episodes.

Discussion

Summar et al[3] and Batshaw et al[6] have identified OTCD as the most common UCD worldwide. Citrullinemia type I was the most common UCD seen in our cohort (20 patients, 34%). This is also supported by another study by Bijarnia et al,[7] which was conducted at a metabolic center in India. Hence, in the Indian population, citrullinemia type I seems to be the most common UCD. It is also the commonest UCD in Turkey, with a prevalence of 13 of 21 total UCDs (62%).[8] Furthermore, in our cohort, 12 patients with citrullinemia type I (52.2%) (24 alleles) had a common mutation (exon 15: c.1168G>A/p.Gln390Arg). This mutation has been reported globally as the most prevalent mutation[9] and, more specifically, was also the single commonest mutation in other populations.[10] The mutation p.Gln390Arg is located in the oligomerization domain of ASS and probably hampers tetramer formation. As ASS functions as a tetramer, a defect in this domain can be expected to be severe, which is supported by the findings in this patient series.

The overall mortality rate was 63.8% in our cohort. We found the mortality rate to be 65.2% in patients with citrullinemia and 83.3% in those with ASA. The most common precipitant was found to be intercurrent infections. Due to the absence of NBS, most of the cases presented to us in a state of severe metabolic decompensation. Moreover, injectable sodium phenylacetate and sodium benzoate are not available in India. Only oral

sodium benzoate is available at select centers, making the administration of emergency protocols difficult.[11] Hence, a high rate of mortality was seen in our cohort compared with the worldwide mortality rates (24%).[6] One study has found 92% 1-year survival rate in a series of 26 children with inborn errors of urea synthesis and 79% of the survivors had one or more developmental disabilities.[12] Another study has reported a mortality rate of 84% for all defects combined in the neonatal presenters,[11,13] whereas in our cohort, it was 69%.

In a retrospective study conducted in Europe, a poor cognitive outcome was observed in patients whose plasma ammonia concentration exceeded 300 µmol/L initially or was 480 µmol/L at its peak.[14] Most of the critically ill children in our study had peak ammonia concentration > 480 µmol/L and they either died or have abnormal neurologic outcome. Many major centers in India do not have in-house testing facilities for plasma ammonia, and samples are sent across cities, wasting time and reducing the reliability of analysis. Moreover, regular ammonia monitoring and keeping a record of it is scarcely available in such critical cases, thereby making predictions about outcome practically impossible. In our observation, newborns presenting with hyperammonemia have ammonia levels generally above 400 µmol/L.

Another important factor for a good neurologic outcome, besides early diagnosis, is regular follow-up and appropriate treatment. In India, sodium benzoate, only for oral treatment, which is usually food grade (not pharmaceutical grade), and L-arginine are available. Sodium phenylbutyrate is not easily available in India.[11] Special amino acid supplements containing all essential amino acids except for arginine, citrulline, and ornithine (UCD diets) are now being manufactured locally, but compliance due to taste and cost is a major issue. Good-quality special amino acid supplements from international brands are expensive and not easily available.

A female child recently diagnosed with OTCD underwent magnetic resonance imaging (MRI) during her admission for hyperammonemia, which revealed gyral swelling involving insular cortices; cingulated gyri; and grey matter of frontal, temporal, and parietal lobes, along with gliotic changes in both the frontal lobes. A follow-up scan for this child has been planned.

The Urea Cycle Disorders Consortium[15] has provided guidelines and suggested MRI with magnetic resonance spectroscopy for regular follow-up of patients with UCD for improving neurologic outcome. However, this modality is barely acceptable by Indian patients because it is expensive. Since genetic disorders including metabolic diseases are not covered under any insurance in India, even the few patients who have such insurance are not eligible for financial support.

All the patients with UCD are subjected to a standard treatment protocol of oral sodium benzoate at a dosage range of 100 to 250 mg/kg/d, L-arginine at a dosage of 250 mg/g/d (except for patients with ARGD), and supplementation of L-citrulline at a dosage of 170 mg/kg/d (for patients with OTCD). Diet is monitored, and low-protein diet along with supplementation of special UCD formula is recommended. Despite attempts to treat patients diagnosed with UCDs, 70% of the patients died. None of these patients were detected by NBS. Five children with citrullinemia type I, 1 with ASA, 3 with OTCD, and 1 with argininemia are being followed up regularly (n = 10) and are under good metabolic control.

One child with citrullinemia type I received an orthotopic liver transplant (OLT) at the age of 6 months and is developing normally both physically and mentally and is on a normal diet, without any episodes of hyperammonemia; however, the orotic acid and citrulline levels in this patient remained consistently high (average citrulline level was > 2000 µmol/L). Whitington et al[16] have documented good recovery in 14 of 16 patients. OLT is an alternative to medical therapy for severe UCDs and OLT results show complete metabolic correction and cessation but not reversal of neurologic deficits.[16] Outcome after OLT is generally very good, and in 2004, there was already an admirable recovery, and 100% survival in 5 children with UCD (2 male children with OTCD, 2 male children with CPS1D, and 1 female child with OTCD who was resistant to medical therapy) was reported.[17]

Two patients with citrullinemia have reached early adolescence and have shown good metabolic control with dietary compliance. These patients are physically normal but mildly affected neurologically, with behavioral problems, hyperactivity disorder, and learning disabilities. Two male children with OTCD are developing well physically but have hyperactivity and learning disabilities. The only child alive with ASA too had initial physical and mental development problems but is now catching up; however, the child has significantly delayed mental milestones and persistently abnormal findings on LFTs. One child with ASA who was diagnosed early in life and was developing normally both physically and mentally, but died due to severe dengue infection associated with severe hyperammonemia (ammonia levels > 3000 μmol/L), which could not be corrected despite dialysis. The child with ARGD has severe developmental delay with spastic diplegia and gets episodic hyperammonemia. He also has severe seizure episodes and mental retardation. He is awaiting a liver transplant.

Two children with citrullinemia type I (patient # 3 and patient # 17), 1 child with OTCD (patient # 30), and 1 child with ARGD (patient # 33) have had multiple seizure episodes, usually generalized tonic and clonic, but these seizures were successfully treated with oral levetiracetam and phenobarbitone. All of them have abnormal findings on EEG. Seizures are common during acute encephalopathy and may be exacerbated by metabolic stressors such as fever or infection.[17] EEG monitoring is recommended in the early course of treatment and during follow-up in acute cases. Seizure activity is thought to be related to hyperammonemic crises or structural damage and subclinical electrographic seizures.[18] Valproate may interfere with the urea cycle and precipitate metabolic crises.[18] EEG is performed more often than MRI in our cohort of patients who are surviving with UCD, and we have found abnormal findings on EEG in 50% of the patients. Gropman et al[2] (number of patients, n = 26) found the incidence of cerebral palsy to be 46%, whereas in our cohort, it was 40% (4 of 10 alive patients) (Table 5). We found no patient with blindness but there is higher incidence of epilepsy in our cohort.

Table 5. Neurologic Outcome

Disorder	Gropman et al[2] (n = 26)	This Study (n = 10)
Normal	—	20%
Cerebral Palsy	46%	40%
Blindness	4%	0%
Epilepsy	17%	50%
Multiple Neurodevelopmental Disabilities	46%	40%

In males with late-onset OTCD, resulting from variants that permit partial enzyme functioning, cognitive outcome is better than in neonatal-onset presenters.[2] In our cohort of 3 patients with OTCD, all were rather late presenters and presumed to have milder variants, especially the male patients. It is possible that in the Indian scenario, where there is no NBS and where the awareness of inborn errors of metabolism is at a very basal level, such neonatal severe forms are not detected, or even if detected, no attempt to treat is made. The common notion among general practitioners and even among pediatricians is that metabolic disorders cannot and should not be treated.

Prenatal diagnosis was performed for 1 couple whose 3 children died of hyperammonemia. The couple was identified to be heterozygous carriers for c.991C>T mutation in exon 4 of *NAGS* gene.

One old retrospective study involving 88 patients has shown that of all the patients, 56% were symptomatic within 4 days of age and 67% within the first week. Thus, prevention of irreversible damage with the help of NBS using blood obtained at 3 to 4 days of life is questionable.[19] Nowadays, the outcomes appear much better.

Conclusions

In India, owing to the absence of NBS, UCDs are detected only after development of symptoms, resulting in a high rate of morbidity and mortality (20 of 34). Citrullinemia is the commonest UCD (23 of 34), with the common mutation p.G390R found in 52.2% of patients. Early and aggressive treatment has resulted in good outcome in at least 2 patients and 4 children were

mildly affected. Unfortunately, 50% of the survivors have epilepsy, 40% have cerebral palsy, and 40% have complex neurobehavioral problems. We did not observe blindness in any of our patients.

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